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Maternal Hyperleptinemia Increases Arterial Stiffening and Alters Vasodilatory Responses to Insulin in Adult Male Mice Offspring

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Abstract

Cardiovascular disease (CVD) is the number one cause of death in the U.S., and exposure to adverse maternal environments has been associated with the development of CVD including hypertension. Gestational diabetes mellitus (GDM) is an adverse maternal environment that has been associated with metabolic and CVD outcomes in the offspring. Key features of GDM and CVD are maternal hyperleptinemia and vascular dysfunction/remodeling, respectively. Yet, there is limited information on the effects of maternal hyperleptinemia on the function and structure of the offspring's resistance vasculature. We hypothesize that alterations in offspring's resistance artery structure and function underlie programming mechanisms for cardiovascular disease that are associated with maternal hyperleptinemia and GDM. To test this hypothesis, we used *Leprdb/+* mice dams, which exhibit maternal hyperleptinemia and wildtype (WT) as controls. Vascular function was assessed in WT male offspring of control and hyperleptinemic dams at 31 weeks of age, after half the offspring had been fed a high fat diet (HFD) for 6 weeks. On a standard diet (SD), offspring of hyperleptinemic dams had mesenteric arteries with larger internal diameters than those of WT dams (258.36 ± 14.99 vs 233.65 ± 9.36 μm , $p < 0.05$) indicative of outwardly remodeled, and enhanced maximal vasodilatory responses to insulin (39.97 ± 6.71 vs 32.23 ± 5.07 %, $p < 0.05$). In offspring of WT, but not hyperleptinemic dams, HFD increased vessel wall cross-sectional area (18590.01 ± 1251.16 vs 12807.20 ± 1060.70 μm^2 , $p < 0.05$), and enhanced the maximal vasodilatory response to acetylcholine (33.74 ± 4.92 vs 21.86 ± 2.73 %, $p < 0.05$). HFD reduced the maximal response to insulin in offspring of hyperleptinemic dams compared to their WT and lean controls (21.88 ± 3.80 vs

37.42±7.84 and 39.97±6.71 % respectively, $p<0.05$). Offspring of hyperleptinemic dams fed a HFD had increased elastic moduli normalized as a function of the percolation of the internal elastic lamina compared to their WT and lean controls (0.53 ± 0.038 vs 0.34 ± 0.023 and $0.38\pm0.032 \times 10^6$ dynes/cm² respectively, $p<0.05$). Offspring of hyperleptinemic dams also had stiffer arteries at high pressure under both dietary conditions (2.36 ± 0.35 vs $1.45\pm0.11 \times 10^6$ dynes/cm², $p<0.05$). We conclude that when mice were fed a SD, maternal hyperleptinemia had beneficial effects to offspring's vascular health, but did not protect offspring fed a HFD. Furthermore, maternal hyperleptinemia induced arterial stiffness in offspring regardless of diet. These results suggest that GDM programs offspring vascular function and structure through mechanisms that may be in part dependent on circulating maternal leptin levels and are differentially affected by postnatal developmental exposures.

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